

## CLAIMS

What is claimed is:

- 1        1. A method for determining the free energy of binding of a potential ligand to a  
2 receptor, comprising the steps of:  
3            obtaining, for each of two or more actual receptor ligands, at least one of a structure  
4 and a free energy of binding to said receptor, such that each of said two or more actual  
5 receptor ligands has a known structure and a known free energy of binding to said receptor;  
6            orienting said structures of said two or more actual receptor ligands for maximum  
7 geometric coincidence with each other;  
8            determining an electrostatic potential at each of more than one point on a van der  
9 Waals surface of each of said actual receptor ligands;  
10          thereafter, mapping each of said electrostatic potentials of each of said actual  
11 receptor ligands onto a geometric surface of one of said two or more actual receptor  
12 ligands, each of said two or more actual receptor ligands being thereby described by an  
13 identical surface geometry but a different electrostatic potential surface, and each of said  
14 electrostatic potentials being described by positional information relating said electrostatic  
15 potentials to said geometric surface;  
16          thereafter, inputting said electrostatic potentials, said positional information, and  
17 said known free energy of binding of one of said two or more actual receptor ligands into  
18 a neural network;  
19          thereafter, training said neural network until said neural network predicts said free  
20 energy of binding of said one of said two or more actual receptor ligands;  
21          repeating said steps of inputting and training for each of the remaining said two or  
22 more actual receptor ligands to produce a trained network;  
23          thereafter, determining a potential ligand electrostatic potential at each of more than  
24 one point on a van der Waals surface of said potential ligand, said potential ligand having  
25 a known structure and an unknown free energy of binding to said receptor;

26       orienting said structure of said potential ligand for maximum geometric coincidence  
27   with said structures of said two or more actual receptor ligands;  
28       thereafter, mapping each of said electrostatic potentials of said potential ligand onto  
29   a geometric surface of one of said two or more actual receptor ligands, said potential ligand  
30   having a surface geometry identical to that of said two or more actual receptor ligands, but  
31   a different electrostatic potential surface, and each of said electrostatic potentials of said  
32   potential ligand being described by positional information relating said electrostatic  
33   potentials to said geometric surface;  
34       thereafter, inputting said electrostatic potentials and said positional information of  
35   said electrostatic potentials of said potential ligand into said trained network; and  
36       using said trained network to calculate a free energy of binding of said potential  
37   ligand to said receptor.

1       2. A method for determining the free energy of binding of a potential ligand to a  
2   receptor, comprising the steps of:  
3       obtaining a structure for said potential ligand;  
4       orienting structures of two or more actual receptor ligands for said receptor for  
5   maximum geometric coincidence with each other;  
6       each of said two or more actual receptor ligands having a known structure and a  
7   known free energy of binding to said receptor;  
8       determining an electrostatic potential at each of more than one point on a van der  
9   Waals surface of each of said actual receptor ligands;  
10      thereafter, mapping each of said electrostatic potentials of each of said actual  
11   receptor ligands onto a geometric surface of one of said two or more actual receptor  
12   ligands, each of said two or more actual receptor ligands being thereby described by an  
13   identical surface geometry but a different electrostatic potential surface, and each of said  
14   electrostatic potentials being described by positional information relating said electrostatic  
15   potentials to said geometric surface;

16 thereafter, inputting said electrostatic potentials, said positional information, and  
17 said known free energy of binding of one of said two or more actual receptor ligands into  
18 a neural network;

19 thereafter, training said neural network until said neural network predicts said free  
20 energy of binding of said one of said two or more actual receptor ligands;

21 repeating said steps of inputting and training for each of the remaining said two or  
22 more actual receptor ligands to produce a trained network;

23 thereafter, determining an potential ligand electrostatic potential at each of more  
24 than one point on a van der Waals surface of said potential ligand, said potential ligand  
25 having an unknown free energy of binding to said receptor;

26 orienting said structure of said potential ligand for maximum geometric coincidence  
27 with said structures of said two or more actual receptor ligands;

28 thereafter, mapping each of said electrostatic potentials of said potential ligand onto  
29 a geometric surface of one of said two or more actual receptor ligands, said potential ligand  
30 having a surface geometry identical to that of said two or more actual receptor ligands, but  
31 a different electrostatic potential surface, and each of said electrostatic potentials of said  
32 potential ligand being described by positional information relating said electrostatic  
33 potentials to said geometric surface;

34 thereafter, inputting said electrostatic potentials and said positional information of  
35 said electrostatic potentials of said potential ligand into said trained network; and  
36 using said trained network to calculate a free energy of binding of said potential  
37 ligand to said receptor.

- 1       3. A computer readable medium, comprising:
  - 2       computer-readable information;
  - 3       said information capable of interacting with a computer to produce an output;
  - 4       said output being a calculated free energy of binding of a potential ligand to a
  - 5       receptor;
  - 6       said output being calculated by:

7               orienting structures of said two or more actual receptor ligands for  
8               maximum geometric coincidence with each other;  
9               each of said two or more actual receptor ligands having a known structure  
10              and a known free energy of binding to said receptor;  
11              determining an electrostatic potential at each of more than one point on a  
12              van der Waals surface of each of said actual receptor ligands;  
13              thereafter, mapping each of said electrostatic potentials of each of said  
14              actual receptor ligands onto a geometric surface of one of said two or more actual  
15              receptor ligands, each of said two or more actual receptor ligands being thereby  
16              described by an identical surface geometry but a different electrostatic potential  
17              surface, and each of said electrostatic potentials being described by positional  
18              information relating said electrostatic potentials to said geometric surface;  
19              thereafter, inputting said electrostatic potentials, said positional information,  
20              and said known free energy of binding of one of said two or more actual receptor  
21              ligands into a neural network;  
22              thereafter, training said neural network until said neural network predicts  
23              said free energy of binding of said one of said two or more actual receptor ligands;  
24              repeating said steps of inputting and training for each of the remaining said  
25              two or more actual receptor ligands to produce a trained network;  
26              thereafter, determining an potential ligand electrostatic potential at each of  
27              more than one point on a van der Waals surface of said potential ligand, said  
28              potential ligand having a known structure and an unknown free energy of binding  
29              to said receptor;  
30              orienting said structure of said potential ligand for maximum geometric  
31              coincidence with said structures of said two or more actual receptor ligands;  
32              thereafter, mapping each of said electrostatic potentials of said potential  
33              ligand onto a geometric surface of one of said two or more actual receptor ligands,  
34              said potential ligand having a surface geometry identical to that of said two or more  
35              actual receptor ligands, but a different electrostatic potential surface, and each of

36        said electrostatic potentials of said potential ligand being described by positional  
37        information relating said electrostatic potentials to said geometric surface;

38            thereafter, inputting said electrostatic potentials and said positional  
39        information of said electrostatic potentials of said potential ligand into said trained  
40        network; and

41            using said trained network to calculate a free energy of binding of said  
42        potential ligand to said receptor.

1        4. A method for determining a free energy of binding of a potential transition-state  
2        inhibitor to an enzyme, comprising the steps of:

3            obtaining, for each of two or more enzyme substrates or inhibitors, at least one of  
4        a structure and a free energy of binding to said enzyme, such that each of said two or more  
5        enzyme substrates or inhibitors has a known structure and a known free energy of binding  
6        to said enzyme;

7            orienting said structures of said two or more enzyme substrates or inhibitors for  
8        maximum geometric coincidence with each other;

9            determining an electrostatic potential at each of more than one point on a van der  
10      Waals surface of each of said enzyme substrates or inhibitors;

11            thereafter, mapping each of said electrostatic potentials of each of said enzyme  
12      substrates or inhibitors onto a geometric surface of a transition state inhibitor, each of said  
13      enzyme substrates or inhibitors being thereby described by an identical surface geometry  
14      but a different electrostatic potential surface, and each of said electrostatic potentials being  
15      described by positional information relating said electrostatic potentials to said geometric  
16      surface of said transition state inhibitor;

17            thereafter, inputting said electrostatic potentials, said positional information, and  
18      said known free energy of binding of one of said two or more enzyme substrates or  
19      inhibitors into a neural network;

20            thereafter, training said neural network until said neural network predicts said free  
21      energy of binding of said one of said two or more enzyme substrates or inhibitors;

22       repeating said steps of inputting and training for each of the remaining said two or  
23   more enzyme substrates or inhibitors to produce a trained network;

24       thereafter, determining an potential transition electrostatic potential at each of more  
25   than one point on a van der Waals surface of said potential transition-state inhibitor, said  
26   potential transition-state inhibitor having a known structure and an unknown free energy  
27   of binding to said enzyme;

28       orienting said structure of said potential transition-state inhibitor for maximum  
29   geometric coincidence with said structures of said two or more enzyme substrates or  
30   inhibitors;

31       thereafter, mapping each of said electrostatic potentials of said potential transition-  
32   state inhibitor onto a geometric surface of one of said two or more two or more enzyme  
33   substrates or inhibitors, such that said potential transition-state inhibitor has a surface  
34   geometry identical to that of said two or more actual receptor transition-state inhibitors, but  
35   a different electrostatic potential surface, and each of said electrostatic potentials of said  
36   potential transition-state inhibitor is described by positional information relating said  
37   electrostatic potentials to said geometric surface of said two or more enzyme substrates or  
38   inhibitors;

39       thereafter, inputting said electrostatic potentials and said positional information of  
40   said electrostatic potentials of said potential transition-state inhibitor into said trained  
41   network; and

42       using said trained network to calculate a free energy of binding of said potential  
43   transition-state inhibitor to said enzyme.

1       5. A method for determining the free energy of binding of a potential transition-  
2   state inhibitor to a enzyme, comprising the steps of:  
3       obtaining a structure for said potential transition-state inhibitor;  
4       orienting structures of two or more enzyme substrates or inhibitors for said enzyme  
5   for maximum geometric coincidence with each other;  
6       each of said two or more enzyme substrates or inhibitors having a known structure  
7   and a known free energy of binding to said enzyme;

8       determining an electrostatic potential at each of more than one point on a van der  
9   Waals surface of each of said enzyme substrates or inhibitors;  
10      thereafter, mapping each of said electrostatic potentials of each of said enzyme  
11   substrates or inhibitors onto a geometric surface of one of said two or more enzyme  
12   substrates or inhibitors, each of said two or more enzyme substrates or inhibitors being  
13   thereby described by an identical surface geometry but a different electrostatic potential  
14   surface, and each of said electrostatic potentials being described by positional information  
15   relating said electrostatic potentials to said geometric surface;  
16      thereafter, inputting said electrostatic potentials, said positional information, and  
17   said known free energy of binding of one of said two or more enzyme substrates or  
18   inhibitors into a neural network;  
19      thereafter, training said neural network until said neural network predicts said free  
20   energy of binding of said one of said two or more enzyme substrates or inhibitors;  
21      repeating said steps of inputting and training for each of the remaining said two or  
22   more enzyme substrates or inhibitors to produce a trained network;  
23      thereafter, determining an potential transition-state inhibitor electrostatic potential  
24   at each of more than one point on a van der Waals surface of said potential transition-state  
25   inhibitor, said potential transition-state inhibitor having an unknown free energy of binding  
26   to said enzyme;  
27      orienting said structure of said potential transition-state inhibitor for maximum  
28   geometric coincidence with said structures of said two or more enzyme substrates or  
29   inhibitors;  
30      thereafter, mapping each of said electrostatic potentials of said potential transition-  
31   state inhibitor onto a geometric surface of one of said two or more enzyme substrates or  
32   inhibitors, said potential transition-state inhibitor having a surface geometry identical to  
33   that of said two or more enzyme substrates or inhibitors, but a different electrostatic  
34   potential surface, and each of said electrostatic potentials of said potential transition-state  
35   inhibitor being described by positional information relating said electrostatic potentials to  
36   said geometric surface;

37 thereafter, inputting said electrostatic potentials and said positional information of  
38 said electrostatic potentials of said potential transition-state inhibitor into said trained  
39 network; and

40 using said trained network to calculate a free energy of binding of said potential  
41 transition-state inhibitor to said enzyme.

- 1        6. A computer readable medium, comprising:
  - 2            computer-readable information;
  - 3            said information capable of interacting with a computer to produce an output;
  - 4            said output being a calculated free energy of binding of a potential transition-state
  - 5 inhibitor to a enzyme;
  - 6            said output being calculated by:
    - 7                orienting structures of said two or more actual receptor ligands for
    - 8                maximum geometric coincidence with each other;
    - 9                each of said two or more actual ligands having a known structure and a
    - 10              known free energy of binding to said enzyme;
    - 11              determining an electrostatic potential at each of more than one point on a
    - 12              van der Waals surface of each of said enzyme substrates or inhibitors;
    - 13              thereafter, mapping each of said electrostatic potentials of each of said
    - 14              enzyme substrates or inhibitors onto a geometric surface of one of said two or more
    - 15              enzyme substrates or inhibitors, each of said two or more enzyme substrates or
    - 16              inhibitors being thereby described by an identical surface geometry but a different
    - 17              electrostatic potential surface, and each of said electrostatic potentials being
    - 18              described by positional information relating said electrostatic potentials to said
    - 19              geometric surface;
    - 20              thereafter, inputting said electrostatic potentials, said positional information,
    - 21              and said known free energy of binding of one of said two or more enzyme
    - 22              substrates or inhibitors into a neural network;

23           thereafter, training said neural network until said neural network predicts  
24        said free energy of binding of said one of said two or more enzyme substrates or  
25        inhibitors;

26           repeating said steps of inputting and training for each of the remaining said  
27        two or more enzyme substrates or inhibitors to produce a trained network;

28           thereafter, determining an potential transition-state inhibitor electrostatic  
29        potential at each of more than one point on a van der Waals surface of said potential  
30        receptor ligand, said potential receptor ligand having a known structure and an  
31        unknown free energy of binding to said enzyme;

32           orienting said structure of said potential transition-state inhibitor for  
33        maximum geometric coincidence with said structures of said two or more enzyme  
34        substrates or inhibitors;

35           thereafter, mapping each of said electrostatic potentials of said potential  
36        transition-state inhibitor onto a geometric surface of one of said two or more  
37        enzyme substrates or inhibitors, said potential transition-state inhibitor having a  
38        surface geometry identical to that of said two or more enzyme substrates or  
39        inhibitors, but a different electrostatic potential surface, and each of said  
40        electrostatic potentials of said potential transition-state inhibitor being described by  
41        positional information relating said electrostatic potentials to said geometric  
42        surface;

43           thereafter, inputting said electrostatic potentials and said positional  
44        information of said electrostatic potentials of said potential transition-state inhibitor  
45        into said trained network; and

46           using said trained network to calculate a free energy of binding of said  
47        potential transition-state inhibitor to said enzyme.

1           7. A method for determining the free energy of binding of a potential ligand to a  
2        receptor according to claim 1, wherein said neural network is a feed forward network with  
3        back propagation of error that learns with momentum.

- 1        8. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 2, wherein said neural network is a feed forward network with  
3 back propagation of error that learns with momentum.
- 1        9. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 4, wherein said neural network is a feed  
3 forward network with back propagation of error that learns with momentum.
- 1        10. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 5, wherein said neural network is a feed  
3 forward network with back propagation of error that learns with momentum.
- 1        11. A computer readable medium according to claim 3, wherein said neural  
2 network is a feed forward network with back propagation of error that learns with  
3 momentum.
- 1        12. A computer readable medium according to claim 6, wherein said neural  
2 network is a feed forward network with back propagation of error that learns with  
3 momentum.
- 1        13. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 7, wherein said neural network uses a learning rate between 0.1  
3 and 0.5 and a momentum term between 0.8 and 0.9.
- 1        14. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 8, wherein said neural network uses a learning rate between 0.1  
3 and 0.5 and a momentum term between 0.8 and 0.9.
- 1        15. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 9, wherein said neural network uses a  
3 learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.
- 1        16. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 10, wherein said neural network uses a  
3 learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

1        17. A computer readable medium according to claim 11, wherein said neural  
2 network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and  
3 0.9.

1        18. A computer readable medium according to claim 12, wherein said neural  
2 network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and  
3 0.9.